



**Fig. 1. Backbone structures of several neuronal nAChR-targeted  $\alpha$ -conotoxins.** A) Structure of  $\alpha$ -conotoxin AuIB determined by NMR. B) Structure of  $\alpha$ -conotoxin [Tyr<sup>15</sup>]EpI determined by X-ray crystallography. C) Structure of  $\alpha$ -conotoxin MII determined by NMR. D) Structure of  $\alpha$ -conotoxin PnIA determined by X-ray crystallography. E) Structure of  $\alpha$ -conotoxin PnIB determined by X-ray crystallography.



**Fig. 2. Gene structure of conotoxins.** Every conotoxin isolated to date has a very conserved gene organization. At the N-terminus (5' end of the gene), there is a signal sequence, followed by a pro region in the middle, and the mature toxin at the C-terminus (3' end of the gene). The signal sequence and pro region are removed by processing during maturation to leave only the mature toxin. Each family of conotoxins (each with a conserved target) shares a completely conserved signal sequence. Thus, the signal sequence is completely predictive of the molecular target of the toxin found at the 3' end of the gene regardless of how divergent it may look from other toxins of the same family.